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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/822,033	03/24/1997	WAYNE A. MARASCO	43471-FWC	5884

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EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	24

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Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
08/822,033	Marasco et al.
Examiner	**Art Unit**
Joseph Woitach	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 26, 2002*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1 and 3-16* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1 and 3-16* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 26, 2002, paper number 41, has been entered.

DETAILED ACTION

This application is a file wrapper continuation of 08/199, 070, filed February 22, 1994.

Applicants' amendment filed November 26, 2002, paper number 42 has been received and entered. Claim 1 has been amended. Claims 1, 3-16 are pending and currently under examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made

to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-5, 7-16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Beug *et al.*, Chaudhary *et al.* and Wu *et al.* for the reasons below and as set forth in the previous office action.

Applicants note the amendment to claim 1 and summarize the nature of a fusion protein produced by recombinant means (page 2). Applicants argue that the combined references of Beug *et al.*, Chaudhary *et al.* and Wu *et al.* teach a chemically conjugated ligand, not a recombinantly made fusion protein comprising an antibody. Further, Applicants argue that nothing in the art supports that use of a recombinant protein would provide greater specificity than a protein made by chemical conjugation as exemplified in a post filing reference by Li *et al.* (2001). Pointing to figures 6C and 7B in the Li *et al.* reference Applicants note a 8 to 10 fold increase higher expression in cells which express the ErbB2 cell surface receptor versus cells which do not express ErbB2 receptor, and argue that an improved selectivity with a targeted recombinant protein was in no way suggested. See Applicants' amendment, pages 2-3. Applicants' arguments have been fully considered, but not found persuasive.

The amendment to claim 1 is noted, in particular that the claims are drawn to a recombinantly produced fusion protein. From the teachings in the present specification a recombinantly produced protein is one which produced as one contiguous protein using conventional and standard molecular techniques known in the art (for example page 24, starting at third full paragraph). Applicants' arguments that a ligand, not an antibody is taught in the combined references is not persuasive because Wu *et al.* specifically teach that an antibody provides an effective means for specifically targeting a fusion protein to a particular epitope on the surface of a desired cell (page 3, lines 7-11). Additionally, Chaudhary *et al.* teach that fusion proteins comprising antibodies and a second protein capable of targeting a desired cell were generated by conventional methods know and used at the time of filing (see example in figure 1). Therefore, the references of both Wu *et al.* and Chaudhary *et al.* specifically provide the necessary teaching for the use of an antibody in the context of a fusion protein to target cell surface receptors on a desired cell.

Applicants' arguments that the combined references provide only for chemical linkage, is not persuasive because Beug *et al.* specifically teach that when the peptides are coupled, for example a ligand to polylysine, recombinant methods can be used to generate the recombinant protein (page 7). Additionally, as noted above, Chaudhary *et al.* teach that fusion proteins comprising antibodies can be generated by conventional methods know and used at the time of filing.

Finally, Applicants arguments that the present invention provides an improved selectivity which wasn't suggested in the art is unpersuasive because the focus of each Beug *et al.*, Chaudhary *et al.* and Wu *et al.* was to provide the targeted delivery of a complex to a cell of interest. In particular, Wu *et al.* demonstrates that providing a targeting moiety in the complex greatly increases the uptake to a cell. Further, the uptake is selective as demonstrated by comparing two human hepatoma cell lines one which contains the cell surface target, HepG2, and one which does not, SHKHep 1 (see figure 1). Chaudhary *et al.* demonstrate the selectivity of a fusion protein complex can range in the exponential scale as demonstrated by uptake and cytotoxicity in OVCAR3 cells (figure 5) or other related cell lines (Table 2). With respect to the improved selectivity demonstrated in the Li *et al.* reference as discussed at page 564, the report of the fold increase in target cells is analogous to that provided by Chaudhary *et al.* and Wu *et al.* comparing cells which have or do not have the targeted cell surface ligand. Additionally, it is noted that in this portion of the Li *et al.* reference the discussion does not focus on the increased selectivity of the complexes, rather 'that the nonviral gene transfer systems reported here disclosed require substantial improvement' (page 564, first full paragraph). Applicants' arguments are not persuasive because at the time of filing the focus of targeted complexes was to increase the uptake of the complex in the target cell. As generally expected, and as demonstrated by Chaudhary *et al.* and Wu *et al.*, recombinant proteins with a targeting moiety are more selectively taken-up by cells which contain the desired target.

In summary, at the time of filing Beug *et al.*, Chaudhary *et al.* and Wu *et al.* provide the necessary teaching for all the embodiments encompassed by the instant claims, and the specific motivation to generate a recombinant targeting protein complex. In particular, where two protein components are provided, such as an antibody coupled to a second protein moiety, there is specific motivation to make this fusion protein recombinantly for the reasons set forth by Wu *et al.* and Chaudhary *et al.* Further, the use of a targeting antibody would generally be accepted to provide a more selective targeting, and as evidenced by Chaudhary *et al.* and Wu *et al.* the selection can be very great. Therefore, for the reasons above and of record, the rejection is maintained.

Claim 6 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Beug *et al.*, Chaudhary *et al.* and Wu *et al.* as applied to claims 1, 3-5, 7-16 above, and in further view of Ryder *et al.* for the reasons below and as set forth in the previous office action.

Applicants argue that the teaching of Ryder *et al.* does not overcome the essential deficiency of Beug *et al.*, Chaudhary *et al.* and Wu *et al.* as discussed for claims 1, 3-5, 7-16. See Applicants' amendment, page 4. Applicants' arguments have been fully considered, but not found persuasive.

As reasoned above, Beug *et al.*, Chaudhary *et al.* and Wu *et al.* provide the necessary teaching and motivation to make obvious claims 1, 3-5, 7-16. Beug *et al.* and Wu *et al.* teach that any variety of polynucleotide binding sequences can be used in forming the complexes and

and attached to the targeting moiety, however specific polynucleotide sequences are not taught. Ryder *et al.* is relied upon to teach that at the time of filing among the various species of sequences recited in claim 6, the Jun DNA binding sequences were known. As noted in the previous office action, Ryder *et al.* is not relied upon to correct deficiencies of Beug *et al.*, Chaudhary *et al.* and Wu *et al.*, rather the teachings are relied upon to teach what was known in the art at the time of filing. Ryder *et al.* provide a detailed teaching for the specific DNA binding sequences and demonstrate that they are effective in binding target DNA as evidenced by the gel shift assay (see results in figure). Applicants' arguments are unpersuasive because Beug *et al.*, Chaudhary *et al.* and Wu *et al.* provide the necessary teaching to make obvious claims 1, 3-5, 7-16, and claim 6 is obvious in light of the teaching of Ryder *et al.* for the specific c-jun DNA binding sequences. Therefore, for the reasons above and of record, the rejection is maintained.

Conclusion

No claim is allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114.

See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Joseph T. Woitach

Deborah Crouch

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PRIMARY EXAMINER
GROUP ~~1800~~ 1630